DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

1533 '99 OCT 25 AM 10:03

OCT 19 1999

Sherokee Ilse
Coalition for Positive Outcomes in Pregnancy
507 Capitol Court, N.E.
Suite 200
Washington, D.C. 20002

Re: Docket No. 98P-0150/CP1

Dear Ms. Ilse:

This letter is in response to your citizen petition (Petition) submitted March 4, 1998, on behalf of the Coalition for Positive Outcomes in Pregnancy (Coalition). You submitted your petition in response to a "Dear Colleague" letter issued on November 13, 1997, by the Food and Drug Administration (FDA) to healthcare providers, warning of the lack of safety and effectiveness data on the prolonged use of subcutaneous terbutaline sulfate via infusion pump in managing preterm labor. You request, among other things, that FDA (1) meet with you and your scientific advisors to discuss the published literature on the use of subcutaneous terbutaline, (2) hold in abeyance the policy stated in the "Dear Colleague" letter, and (3) take no additional action to prohibit physicians' use of terbutaline in any form.

FDA reaffirms the position stated in the "Dear Colleague" letter that there is no evidence of the effectiveness of prolonged treatment with subcutaneous terbutaline to manage preterm labor and that there are significant safety concerns associated with unmonitored, long-term administration of the drug. Regarding your individual requests, FDA grants your petition in part and denies it in part for the reasons set forth below.

I. DISCUSSION OF ISSUES RAISED IN THE PETITION

A. Data on the Efficacy of Long-Term Use of Subcutaneous Terbutaline

You maintain that terbutaline has been safely and effectively used to treat preterm labor for over twenty years with well-documented benefits and side effects. In support of this position, you cite a 1988 report by the American College of Obstetricians and Gynecologists (ACOG), statements at the October 1992 and May 1993 meetings of FDA's Fertility and Maternal Health Advisory Committee, and a 1995 ACOG Technical Bulletin (Petition at 3-5). You also refer to medical literature published since the May 1993 advisory committee meeting that you believe supports your contention that subcutaneous terbutaline is safe and effective for treating preterm labor (*id.* at 5-8).

Prior to issuing the "Dear Colleague" letter, FDA considered the advisory committee conclusions and ACOG documents that you cite. The Agency continues to believe that they do not provide support for the prolonged use of subcutaneous terbutaline in managing preterm

98P-0150

PAV 1

labor. Although the advisory committee concluded that terbutaline administered intravenously appeared to have an acceptable risk-benefit profile for the acute treatment of preterm labor under limited circumstances (i.e., in pregnancies of 33 weeks gestation or less, when cervical dilation is 4 centimeters or less and there is no premature rupture of membranes, and with careful maternal and fetal monitoring),[1] it could not reach the same conclusion about subcutaneous terbutaline. The ACOG Technical Bulletin you cite noted that subcutaneous terbutaline was associated with adverse events similar to those seen with intravenous use of terbutaline, although with less frequency. However, the data on which that assessment was made are difficult to interpret, due to the uncertainties inherent in the reporting of adverse events and the largely observational nature of the published literature on subcutaneous terbutaline.

As the "Dear Colleague" letter notes, no long-term tocolytic benefit (i.e., beyond 48 to 72 hours) has ever been consistently demonstrated for terbutaline or any beta-agonist. Further, other than providing a brief opportunity for administration of maternal glucocorticoids or transfer to a tertiary care facility, the data do not support any measurable infant benefit from treatment with beta-agonist tocolytics.[2] There is no conclusive evidence that the use of terbutaline by any method of administration produces consistent benefits in gestational age at delivery, birth weight, neonatal morbidity, or perinatal morbidity. In fact, most studies offer evidence suggesting that there are no such benefits.

The published literature on the effectiveness of terbutaline administered subcutaneously to manage preterm labor is confined to observational studies, generally without the benefit of randomization or controls. Those studies that are controlled are either very small, lacking the statistical strength to support any conclusion, or published only in abstract form. Following are comments on the studies you reference (Petition at 6-7) concerning the safety and effectiveness of subcutaneous terbutaline that have been reported since the May 1993 advisory committee meeting:

(1) Allbert et al. examined the efficacy of subcutaneous terbutaline in 992 women and reported that pregnancy was prolonged an average of 7 weeks (with treated patients delivering, on average, at 36 weeks' gestation).[3] This study is a

---

[1]Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting, May 21, 1993, at 181-183.

[2]Canadian Preterm Labor Investigators Group, "Treatment of Preterm Labor With the Beta-Adrenergic Agonist Ritodrine," *New England Journal of Medicine*, 327:308-312, 1992; J.F. King et al., "Beta-Mimetics in Preterm Labour: An Overview of the Randomized Clinical Trials," *British Journal of Obstetrics and Gynecology*, 95:211-212, 1988.

[3]J.R. Allbert et al., "Tocolysis for Recurrent Preterm Labor Using a Continuous Subcutaneous Infusion Pump," *Journal of Reproductive Medicine*, 39:614-618, 1994.

retrospective record review, and the authors do not describe how records were selected. Further, the only eligibility criterion for treatment was any magnitude of cervical change, putting patients at variable risk for preterm delivery.

(2) The study by Elliott et al. of terbutaline administered via subcutaneous infusion pump is a nonrandomized, noncomparative observational study of use of the drug in high-order multiple gestations.[4]

(3) The study by Perry et al. is a retrospective chart review, much like that of Allbert et al. As in the Allbert study, the authors do not clearly specify their criteria for chart selection, a major potential bias in the ascertainment of outcomes.[5]

Only two of the studies you cite involve controlled trials of subcutaneously administered terbutaline for tocolysis. One is an abstract; the other is a very small study with equivocal results:

(1) A study by Wenstrom et al. randomized patients with protocol-defined progressive cervical change to terbutaline by subcutaneous pump (blinded), saline by subcutaneous pump (blinded), or oral terbutaline once preterm labor was arrested with intravenous magnesium.[6] In all, 42 patients were randomized, and the mean gestational age at delivery and neonatal outcomes were the same in all three groups. This study is very small, and while the authors conclude that the three maintenance treatment arms appear equivalent, the statistical strength of that equivalence is not robust and conclusions are difficult to reach. Interestingly, however, the authors conclude that the terbutaline pump should remain experimental.

(2) An abstract of a study by Lam et al., presented at the Society of Perinatal Obstetrics annual meeting in January 1998, describes a trial in which 256 patients who failed oral terbutaline received subcutaneous terbutaline and

---

[4]J.P. Elliott et al., "Terbutaline Pump Tocolysis in High-Order Multiple Gestation," *Journal of Reproductive Medicine*, 42:687-694, 1997.

[5]K.G. Perry et al., "Incidence of Cardiopulmonary Effects With Low-Dose Continuous Terbutaline Infusion," *American Journal of Obstetrics and Gynecology*, 173:1273-1277, 1995.

[6]K.D. Wenstrom et al., "A Placebo Controlled Randomized Trial of the Terbutaline Pump for Prevention of Preterm Delivery," *American Journal of Perinatology*, 14(3):87-91, 1997.

subsequently experienced prolonged gestation.[7] The abstract does not permit consideration of the study's design or findings in any depth or detail. Therefore, we are unable to draw any conclusions about the study's methodological merit or its findings.

In conclusion, FDA finds that there is insufficient scientific support for a claim that use of terbutaline administered by continuous, subcutaneous infusion pump results in improved preterm labor treatment outcomes.

B. Data on the Safety of Long-Term Use of Subcutaneous Terbutaline

As described above, convincing data on the efficacy of prolonged use of subcutaneous terbutaline in the management of preterm labor do not exist. In addition, there are serious safety concerns associated with such use. The toxicity profile of terbutaline is well-known and similar whether the drug is administered subcutaneously, orally, or intravenously. Lower doses of terbutaline can be administered subcutaneously to produce the same pharmacological effects as oral terbutaline in patients with bronchospasm because the drug is more bioavailable in subcutaneous rather than oral form. For example, an oral dose of 5 milligrams leads to serum levels similar to those of a subcutaneous dose of 0.25 milligrams. The toxicity profile for each mode of administration is essentially the same.

Published reports on the use of continuous, subcutaneous terbutaline cite incidences of pulmonary edema, cardiac arrhythmia, tachycardia, diaphoresis, extreme tremors, hypertension, and other known toxicities and side effects of the drug.[8] Unfortunately, there has been no attempt to compare incidences of these adverse events in a prospective, randomized study. The reports describe a variety of dosing strategies, with no standardization or attempt to correlate dosing with the known pharmacokinetics and pharmacodynamic activity of the drug. Such correlations are critical to ensuring the safety of any drug administered parenterally in an outpatient setting.

You cite the study by Perry et al. as evidence of the better safety profile of subcutaneous

---

[7]F. Lam et al., "Pregnancy Prolongation and Route of Tocolytic Administration in Patients With Singleton Gestation," *American Journal of Obstetrics and Gynecology*, 178:180, 1998.

[8]D.L. Levy, "Morbidity Caused by Terbutaline Infusion Pump Therapy," *American Journal of Obstetrics and Gynecology*, 170:1835, 1995; P.G. Quinn et al., "Terbutaline Hepatitis in Pregnancy," *American Journal of Gastroenterology*, 89:781-784, 1994; D.R. Hudgens and S.E. Conradi, "Sudden Death Associated With Terbutaline Sulfate Administration," *American Journal of Obstetrics and Gynecology*, 160:120-121, 1993; K.J. Moise et al., "Continuous Subcutaneous Terbutaline Pump Therapy for Premature Labor: Safety and Efficacy," *Southern Medical Journal*, 85:255-260, 1992; J.R. Fischer and B.L. Kaatz, "Continuous Subcutaneous Infusion of Terbutaline for Suppression of Preterm Labor," *Clinical Pharmacy*, 10:292-296, 1991.

terbutaline (Petition at 6). However, as noted above, the authors' failure to specify their criteria for chart selection creates a major potential bias in the ascertainment of outcomes. Interestingly, the overall spectrum of toxicity reported in the study is the same as is described in all other studies of terbutaline. Patient predictors of these events are not reliable, with the exception of cardiac arrythmias, which are more likely in patients with underlying cardiac electrical aberrancies. In addition to the fetal and other maternal monitoring requirements for patients in preterm labor, the toxicities of terbutaline remain an important reason for prescribing standard, in-hospital administration.

II. RESPONSE TO SPECIFIC REQUESTS

You request that FDA take several specific actions regarding the use of terbutaline for managing preterm labor (Petition at 2). Following are the Agency's responses to your requests.

A. That FDA Review the Published Studies Referenced in the Petition

You ask that FDA review the published clinical data that you reference in the petition. FDA has reviewed the published data on the safety and effectiveness of terbutaline for managing preterm labor, including the more recent studies you cite in the petition. Having conducted this review, the Agency reiterates its position, as set forth in the "Dear Colleague" letter, that the value of tocolytics in general is limited to an initial, brief (approximately 48 to 72 hours) period of treatment. There is no evidence of a benefit from prolonged treatment with any form of terbutaline, including subcutaneous administration. Moreover, the published literature on the safety and efficacy of subcutaneous terbutaline remains confined to observational studies, generally without the benefit of randomization or contemporary controls.

B. That FDA Immediately Meet With Petitioner to Discuss the Clinical Studies on Subcutaneous Terbutaline to Determine Whether Methodological Inadequacies Are Present

You request that FDA immediately meet with you and your scientific advisors to discuss whether there are methodological inadequacies in the clinical studies on subcutaneous terbutaline you cite. As discussed above, the studies to which you refer are largely observational in nature. Consequently, the data from these studies are difficult to interpret and lack reliability. However, if you are aware of other non-observational studies that you believe support the efficacy of subcutaneous terbutaline for treating preterm labor, we invite you to submit reports of such studies for FDA's review. The Agency would consider having a follow-up meeting with you if warranted by the new data.

C. That if There Are No Significant Inadequacies, the Data Be Presented to the Advisory Committee as Soon as Possible

You request that FDA present the data from the studies on subcutaneous terbutaline to the advisory committee if there are no significant inadequacies. Because FDA finds that the data in the published literature are inadequate to allow conclusions to be drawn about the safety and effectiveness of subcutaneously administered terbutaline, the Agency does not believe it would be productive to present data to the advisory committee at this time. Should substantial data from a well-designed, randomized, controlled clinical trial become available, we will give serious consideration to presenting the data to the committee.

D. That FDA Hold in Abeyance the Policy Stated in the "Dear Colleague" Letter Until Discussions Occur and So Notify Recipients of the Letter

You ask that FDA hold in abeyance the policy stated in the "Dear Colleague" letter until discussions occur and that the Agency notify the recipients of the letter of this action. For the reasons stated above, FDA reaffirms the positions stated in the "Dear Colleague" letter. Consequently, there is no need to contact the healthcare professionals who received the letter.

E. That FDA Take No Additional Action to Prohibit the Use of Terbutaline by Physicians Until Scientific Discussions Occur

You request that FDA take no additional action to prohibit the use of terbutaline in any form in the practice of medicine until scientific discussions occur. FDA has taken no action that would prohibit the use of any form of terbutaline by physicians in the practice of medicine, including treating preterm labor. In general, once FDA has approved a drug product for marketing, a physician may, as part of the practice of medicine, prescribe it for uses or in treatment regimens or patient populations that are not included in the approved labeling. Nonetheless, when an unapproved use is promoted, becomes widespread, or endangers the public health, the Agency has an obligation to provide medical practitioners with the best information available to make sound therapeutic decisions. It is important that physicians who treat preterm labor be fully aware that, despite the technology available to administer terbutaline subcutaneously and commercial services that promote such use, there are no controlled studies of prolonged administration of subcutaneous terbutaline sulfate that establish the safety and effectiveness of the drug in treating preterm labor beyond 48 to 72 hours. This is especially relevant when subcutaneous terbutaline is provided under conditions, such as prolonged outpatient administration, that do not afford the maternal and fetal monitoring appropriate for the drug's known toxicity profile.

F. That FDA Require Manufacturers of Terbutaline to Remove From Labeling the Warning and Precaution Statements Against Use in Preterm Labor

You request that FDA require the manufacturers of terbutaline (approved for use as a bronchodilator) to remove the labeling statements (appearing in the PRECAUTIONS and WARNINGS sections) against the use of terbutaline for managing preterm labor. (The PRECAUTIONS section of the package inserts for Novartis' Brethine products states that "terbutaline sulfate should not be used for tocolysis"; the WARNINGS section of the inserts for Hoechst Marion Roussel's Bricanyl products states that the products are "not indicated and should not be used for the management of preterm labor.") FDA has worked with the manufacturers of terbutaline to address the need for clarification and characterization of the uses and risks of terbutaline. FDA remains willing to review a supplemental application for a tocolytic indication for terbutaline as well as revisions to terbutaline labeling concerning use in managing preterm labor. However, the Agency has no basis at this time to require terbutaline manufacturers to remove statements about tocolysis from existing package inserts.

G. That FDA Grant Accelerated or Fast-Track Review to New Drugs and Therapies for the Treatment and Prevention of Preterm Labor

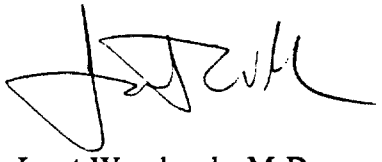
Finally, you ask that FDA grant accelerated or fast-track review to new drugs for the treatment and prevention of preterm labor. Please be assured that FDA is keenly aware of the need for safe and effective tocolytic agents. The Agency has worked intensively with sponsors who seek to develop new tocolytics and will continue to do so. Moreover, we will strongly consider granting priority review status to any new drug application that we receive for a tocolytic agent.

III. CONCLUSION

FDA disagrees with your conclusion that there is sufficient evidence demonstrating that terbutaline administered subcutaneously is safe and effective for treating preterm labor and prolonging pregnancy. Having reviewed the studies you reference in the petition, the Agency finds nothing that warrants changing the position stated in the November 1997 "Dear Colleague" letter that continuous, subcutaneous administration of terbutaline for preterm labor has not been demonstrated to be effective and is potentially dangerous. Consequently, the Agency concludes that no benefit would be obtained at this time from meeting with you to discuss the published literature on terbutaline or from presenting existing data to the advisory committee. However, the Agency would be willing to review any new data from clinical studies on subcutaneous terbutaline should such data become available.

Therefore, for the reasons stated above, FDA denies the requests set forth in your petition except as specified otherwise.

Sincerely yours,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research